THE NATURAL HISTORY OF ACUTE DILATED CARDIOMYOPATHY

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ABSTRACT

Introduction. Acute dilated cardiomyopathy (ADCM) is a frequent cause for referral for cardiac transplantation yet its prognosis and natural history on contemporary therapy remain uncertain.

Methods. The Multicenter Intervention in Myocarditis and Acute Cardiomyopathy (IMAC)-2 trial enrolled 373 patients at 12 academic medical centers with left ventricular ejection fraction (LVEF) $\leq$ 40%, heart failure symptoms $<$ 6 months duration, and a diagnostic evaluation consistent with idiopathic cardiomyopathy or acute myocarditis. The natural history of ADCM in an earlier era (1975–2000) was also examined via a MEDLINE search of published observational studies.

Results. Mean age of the IMAC-2 study cohort was 45 $\pm$4 years and 38% were female. Mean initial LVEF was 24% $\pm$ 8% and increased to 40% $\pm$ 12% during treatment with ACE-I/ARB (82%), and a beta-blocker (94%). Transplantation-free survival at 1, 2, and 4 years was 94%, 92%, and 86%, respectively. This survival rate was substantially higher than the prior era. Multivariate predictors of improvement in LVEF were smaller LV dimension and higher systolic blood pressure whereas black race and higher initial New York Heart Association functional class were associated with lower final LVEF. Genotypic variation did not correlate with response to pharmacological therapy.

Conclusion. Earlier diagnosis and aggressive pharmacologic and device-based therapy of ADCM has led to improved prognosis.

INTRODUCTION

Idiopathic dilated cardiomyopathy (IDCM) of acute onset is a primary myocardial disease of unknown cause characterized by impaired ventricular contractility and ventricular dilatation; it is the most com-

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mon cause of systolic heart failure in young adults (1). The age-adjusted prevalence of IDCM in the United States averages 36 cases per 100,000 population. Differentiation of IDCM from secondary and potentially reversible forms of myocardial disease (e.g., alcohol-related cardiomyopathy, endocrine disorders, and infectious etiologies) has important prognostic and therapeutic implications (2). A detailed evaluation of acute onset dilated cardiomyopathy (ADCM) typically does not elucidate a specific etiology in more than 50% of cases (2). Fortunately, partial or complete myocardial recovery may occur in more than one-third of ADCM cases.

PATHOGENESIS

Several mechanisms have been postulated for its pathogenesis: 1) familial and genetic factors, 2) viral myocarditis and other cytotoxic insults, and 3) immunologic abnormalities. These mechanisms are not mutually exclusive and several may combine to produce clinical disease in susceptible individuals.

Genetic Causes

Familial disease has been reported to occur in up to 25% of patients and at least one first-degree relative with decreased ejection fraction has been reported in many families (3). No clinical or histopathologic characteristics distinguish familial from nonfamilial disease. The mode of inheritance is most frequently autosomal dominant but the disease is genetically heterogeneous with reports of autosomal recessive, X-linked recessive, and mitochondrial inheritance. Specific genetic mutations have been reported in sarcomeric proteins, cytoskeletal support proteins, nuclear envelope proteins, the spliceosome, and mitochondria (4). Recently, truncations in the protein titin have been reported in a significant portion of IDCM cases (5).

Viral Myocarditis and Cytotoxic Insults

ADCM is believed to be caused by viral myocarditis in approximately 10% to 15% of patients; differentiating between the two conditions based on initial clinical or echocardiographic findings is often impossible (6). It is believed that an autoimmune response triggered by aberrations in the induction of major histocompatibility antigen expression is responsible for both the initial insult and disease progression (1). Myocarditis is a histopathologic diagnosis obtained via endomyocardial biopsy or, at the time of cardiac explantation, and is

defined by the presence of an inflammatory cellular infiltrate, myocyte necrosis, and/or degeneration, or immunohistochemical abnormalities. Immunohistochemistry is replacing the prior Dallas criteria in the diagnosis of myocarditis. Monoclonal antibodies allow characterization and localization of mononuclear cell infiltrates (e.g., CD3 for T cells, CD68 for activated macrophages) and human leukocyte antigen (HLA)-DR-α to assess HLA class II expression (6). With the use of these more sensitive immunohistologic methods, the frequency with which biopsy reveals myocarditis has increased (6).

IMMUNOLOGIC ABNORMALITIES

Circulating autoantibodies to a variety of cardiac antigens have been identified, including those to the β_1-adrenergic receptor, alpha-myosin autoantibodies, and mitochondrial antigens such as adenine nucleotide translocator, and adenosine diphosphate-adenosine triphosphate carrier proteins (1). Anti-heart antibodies have been detected in more than one third of first-degree relatives of patients with ADCM who had normal echocardiographic findings at the time (7). Importantly, relatives with circulating anti-heart antibodies have a 20-fold higher likelihood of developing overt dilated cardiomyopathy over the next decade. Whether these autoantibodies are truly pathogenic or merely reflect long-term myocardial injury is unknown. Decreased activity of natural lymphocyte killer cells (which are an antiviral defensive mechanism), upregulation of F_cII_A receptors on cardiomyocytes, and HLA class II antigens have also been reported (8). The hypothesis that ADCM is an immunologically mediated disorder is partially supported by these associated findings (1).

CLINICAL PRESENTATION

The most common initial manifestation of ADCM is symptomatic heart failure which occurs in more than 75% of patients (1). Chest pain, sometimes indistinguishable from classic angina pectoris, occurs as an initial symptom in 8% to 20% of patients (1). Coronary vascular reserve is more limited in such patients than those who have ADCM without chest pain. Systemic or pulmonary emboli are rare initial manifestations observed in fewer than 5% of cases and usually occur in patients with more advanced heart failure and cardiomegaly (1). Ventricular arrhythmias are common but syncope and sudden death are rare initial manifestations of disease.

NATURAL HISTORY FROM PRIOR PUBLISHED STUDIES

The natural history of ADCM in an earlier era (1975–2000) was examined via a MEDLINE search of published observational studies. Initial reports from tertiary referral centers reported a mortality rate of 25% to 30% at 1 year and approximately 50% at 5 years (1). The poor survival rates reported in these early studies almost certainly reflected a major referral bias because patients with more advanced disease or treatment failures were more likely to be referred. Steimle et al identified shorter duration of symptoms, higher serum sodium concentration, and lower intracardiac filling pressures as independent predictors of spontaneous improvement in left ventricular ejection fraction (LVEF) by multivariate analyses (9). Initial LVEF did not predict subsequent recovery and did not correlate with final LVEF.

THE IMAC II TRIAL

The natural history of ADCM using contemporary therapy is even less well known. The Intervention in Myocarditis and Acute Cardiomyopathy (IMAC)-2 trial was a prospective multicenter investigation of myocardial recovery in subjects with recent onset (i.e., acute) nonischemic cardiomyopathy (10). Subjects were enrolled at 12 centers and all had LVEF $\leq$ 40% by echocardiography and cardiac symptoms $\leq$ 6 months duration.

Study Population

Demographic information, including self-designated race (white, black, Asian, or other) was collected and angiographic or noninvasive testing was performed to exclude occult coronary artery disease. Patients with significant diabetes mellitus (requiring therapy with insulin or an oral agent for greater than 1 year), uncontrolled hypertension (diastolic blood pressure $>$ 95 mm Hg or systolic blood pressure $>$ 160 mm Hg), suspected alcohol-related cardiomyopathy, tachycardia-related cardiomyopathy, uncorrected thyroid disease or a systemic disease known to be associated with dilated cardiomyopathy (e.g., sarcoidosis, hemochromatosis) were excluded. Right ventricular endomyocardial biopsy was not required for enrollment. Left ventricular size and function were assessed at entry and at 6 months; patients were followed for up to 48 months after enrollment. All deaths and hospitalizations were adjudicated by an independent events committee. The primary outcome was change in LVEF from baseline to 6

months. Secondary endpoints included transplant-free survival and hospitalization-free survival.

Statistical Analysis

Demographic and clinical characteristics were compared by sex and race (black versus non-black) with continuous variables compared by Student *t* test and categorical variables compared by the use of the Fisher exact test. In multivariate analysis, multiple linear regression was used to identify independent predictors of change in LVEF at 6 months. Covariates were selected by use of a stepwise selection (forward) with an entry and a retainment *P* value of .05. Statistical analytic methods were based on three endpoints: death, death or transplant, and composite endpoint including death, transplantation, or heart failure hospitalization. Kaplan-Meier analysis was used to estimate event-free survival and curves were compared by log rank test.

Results

The cohort comprised 373 consecutive patients including 39 (10%) women with peripartum cardiomyopathy. The mean age was 45 ± 14 years and initial LVEF was 24% ± 8%. Symptom duration averaged 2.2 ± 1.7 months and New York Heart Association (NYHA) functional class at entry was I (18%), II (46%), III (29%), or IV (7%), respectively. There were 21% black and 38% women included in the trial. Forty-four (12%) subjects underwent endomyocardial biopsy; myocardial inflammation was observed in 4% of subjects and unequivocal myocarditis diagnosed in only 2.6% of those biopsied.

Baseline therapy included an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (91%), beta-adrenergic blocker (82%), loop diuretic (67%), and an aldosterone receptor antagonist (27%). At entry, 7.5% of patients had an implantable cardioverter defibrillator; 7.5% were receiving intravenous inotropic therapy, and 2.4% were supported with an intra-aortic balloon pump or a left ventricular assist device. Therapy was intensified during the follow-up period; pharmacologic treatment included an ACE inhibitor or angiotensin receptor blocker (92%), beta-adrenergic blocker (94%), and implantable defibrillator (20%) at 6 months.

Change in LV Function

The mean LVEF at 6 months increased to 40% ± 12%. Overall, 70% of subjects showed an increase ≥ 10 ejection fraction units; and 39%

showed an increase ≥ 20 EF units; LVEF normalized (LVEF > 50%) in 25% of patients. At 6 months, NYHA functional classes were I (44%), II (45%), III (9%), and IV (1%), respectively. The percent of subjects in whom LEVF normalized differed by sex (men 20%, women 34%) (P = .004). There was a trend towards less recovery in blacks (18%) versus non-blacks (27%; P = .14).

Clinical Outcomes

The mean follow-up was 2.2 ±1.4 years. During this time, there were 14 deaths (4%) and 17% of patients underwent heart transplantation (5%). Overall, 45 hospitalizations for decompensated heart failure occurred (12%). Survival rates at 1, 2, and 4 years were 98%, 96%, and 94%, respectively. Transplantation-free survival was 94%, 92%, and 88%, respectively (Figure 1A). Prognosis was dependent on functional class at initial clinical presentation (Figure 1B). Myocardial recovery was more evident in women and transplantation-free survival was consequently significantly better in women, averaging 96% at 4 years compared to 84% for men (P = .03). Although medical therapy was comparable between cohorts, black subjects had poorer clinical outcomes. Transplantation-free survival rates for blacks at 1, 2, and 4 years were 90%, 85%, and 72%, respectively, compared to 95%, 93%, and 92% for non-blacks (P = .01), respectively.

Relationship of Heart Size and Recovery

At study entry, the mean left ventricular end-diastolic dimension (LVEDD) was 6.3 ± 1.0 cm. The degree of ventricular enlargement correlated with subsequent improvement in ejection fraction during treatment. LVEF increased in the cohort with mild ventricular enlargement from 27 ± 8% to 45 ± 11%. In contrast, among patients with severe ventricular enlargement, LVEF only increased from 20 ± 7% to 32 ± 12%. A similar association of smaller LVEDD with greater recovery was evident in both men and women.

Predictors of Improvement

Multivariate predictors of improvement in LVEF at 6 months were smaller LVEDD at baseline and higher baseline systolic blood pressure. Black race and higher NYHA classification were associated with lower LVEF at 6 months. This association was noted to be independent of baseline ejection fraction which was included as a covariate and was

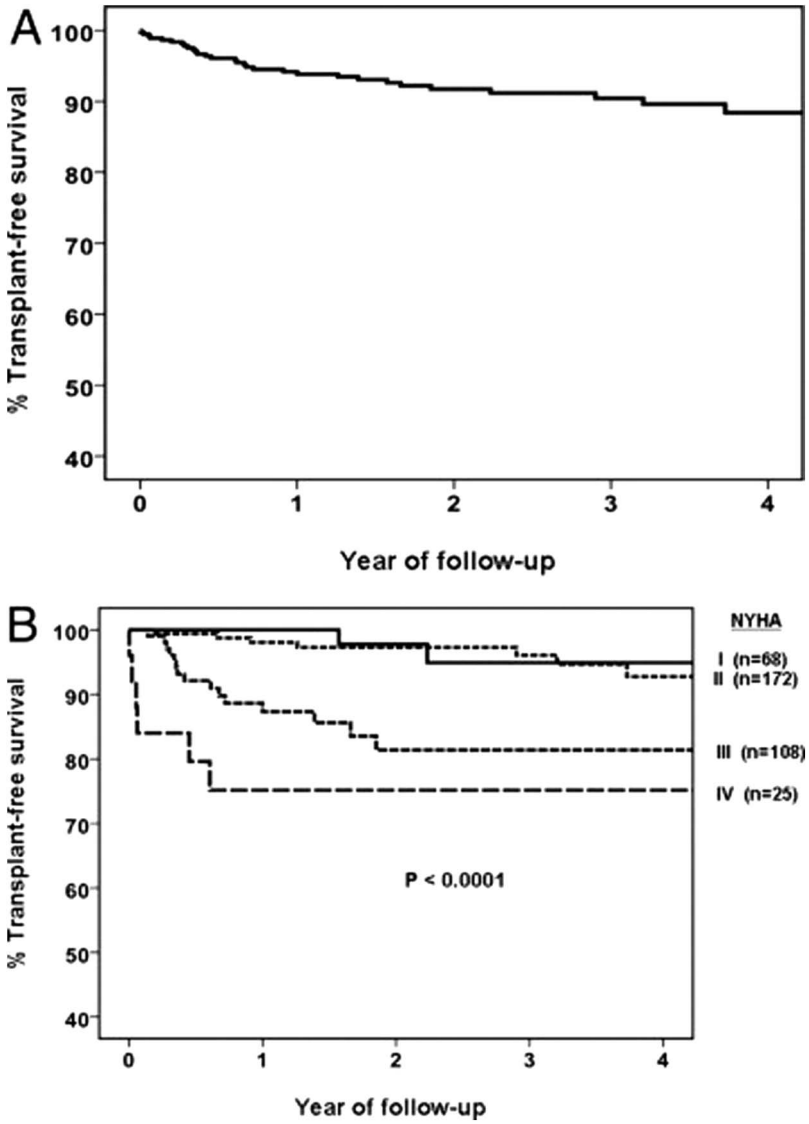

FIG. 1. **(A)** Freedom from death or cardiac transplantation in new onset dilated cardiomyopathy. **(B)** Freedom from death or cardiac transplantation by New York Heart Association functional class at initial presentation. (From McNamara D, et al. *J Am Coll Cardiol* 2011;58:1114; used with permission.)

not associated with LVEF at 6 months ($P = .32$). In total, seven variables included in the multiple linear regression analysis explained 25% of the variation in LVEF at 6 months.

DIAGNOSTIC EVALUATION IN ADCM

Echocardiography is the most useful initial diagnostic test. Impaired ventricular contractility is the sine qua non of DCM and a left ventricular ejection fraction $\leq 40\%$ is required for diagnosis. Although global hypokinesis is often observed, considerable segmental wall motion variability is evident in more than 50% of patients due to altered regional wall stress and abnormal regional myocardial metabolism (1). Right ventricular dysfunction is present early in the course of the disease in a substantial minority of patients ($<30\%$) but is highly associated with adverse prognosis (11).

Serum biomarkers are useful in establishing the diagnosis and helping to define prognosis. B-type natriuretic peptide is almost always increased when significant left ventricular dysfunction exists; it also provides a serial noninvasive marker for assessing response to therapy. Similarly, troponin I or T may be persistently increased in ADCM patients despite the absence of coronary artery disease or biopsy-proven myocarditis. Patients who have persistent low-grade circulating troponin levels have a substantially poorer prognosis despite similar ejection fraction and NYHA functional class compared to patients who have initial elevations that subsequently normalized or those who have never had elevation in serum troponin levels (12).

Multivessel coronary artery disease may present with global left ventricular dysfunction mimicking primary heart muscle disease. Computer tomographic coronary imaging should be considered for patients with chest pain, coronary risk factors, diabetics, or individuals older than the age of 45 to 50 years (13).

Cardiac magnetic resonance imaging (cMRI) has become increasingly important in the diagnosis of new-onset cardiomyopathy. cMRI may establish a normal coronary blood flow pattern and T1 imaging is highly sensitive in detecting myocardial injury and edema. cMRI should be considered for patients in whom an endomyocardial biopsy is being considered. It is useful in differentiating cardiac sarcoid from other forms of dilated cardiomyopathy (14). The extent of late gadolinium enhancement (LGE) correlates closely with the amount of myocardial scar/fibrosis. The percent LGE correlates quite closely with subsequent clinical outcome (15). Those individuals with more extensive late enhancement have a 2- to 3-fold worse prognosis than those with similar ejection fraction who have minimal or no late enhancement (15, 16).

Finally, endomyocardial biopsy is occasionally indicated in patients with ADCM. Current practice guidelines suggests that it is useful for patients with new onset cardiomyopathy in whom allergic/eosinophilic

myocarditis, cardiac sarcoidosis, or giant cell myocarditis are suspected (17). The low diagnostic yield has led to a decline in its use (<10%) combined with the lack of proven efficacious therapy for lymphocytic myocarditis has led to substantial decrease in the use of this invasive technique. Biopsy can be useful for detecting treatable systemic diseases known to affect the myocardium such as sarcoid or eosinophilia (1, 17). It is also useful in the research setting for elucidating potential molecular bases for ADCM.

TREATMENT

Pharmacologic therapy should include a vasodilator, in the form of either an ACE inhibitor or angiotensin receptor blocker as well as a beta-adrenergic blocker. These two agents should be used in both symptomatic and asymptomatic left ventricular dysfunction. It remains controversial whether pharmacologic therapy should be continued indefinitely among patients who normalize their ventricular function. Diuretics should be used judiciously for controlling heart failure symptoms but should be avoided in patients who have asymptomatic left ventricular dysfunction.

The role of anticoagulation among patients with ADCM and sinus rhythm continues to generate controversy. Such patients have a theoretically increased risk of systemic and/or pulmonary embolism because of blood stasis and low flow in the hypocontractile ventricle. Systemic anticoagulation with warfarin should be reserved for patients who have chronic or paroxysmal atrial fibrillation or a documented left ventricular thrombus.

Although asymptomatic, nonsustained ventricular tachycardia is commonly observed in ADCM patients who undergo ambulatory electrocardiographic monitoring, its pharmacological suppression does not improve prognosis. Implantable cardioverter defibrillator therapy should be considered for ADCM patients who show persistent depression of left ventricular ejection fraction less than 30% after at least 6 months of optimized pharmacologic therapy (1). Unloading the failing myocardium with a left ventricular assist device has been reported to promote myocardial recovery in a minority (<5%) of patients who have severe ADCM (18).

A variety of molecular abnormalities have been described in ADCM. Genes may be introduced into the failing myocardium with nontoxic viral vectors and result in improved ventricular contractile function. Studies in animals and small numbers of clinical trials are currently evaluating genes that manipulate the myocardial beta-

adrenergic receptor system, modify G protein-coupled receptor kinase, activate cardiac adenylate cyclase-6, and inhibit crucial proapoptotic pathways (19). The most promising approach appears to be overexpression of sarcoplasmic calcium ATPase (SERCA 2A) (18). Animal models have shown a long-term expression of SERCA 2A by intracoronary delivery of adeno-associated viral vector. This approach has been associated with improved systolic function and favorable ventricular remodeling in a swine-volume overload model. The ongoing *Calcium Up-regulation* by *Percutaneous* administration of gene therapy *In* cardiac *Disease (*CUPID) trial is now evaluating the clinical utility of this gene-based strategy. It is hoped that specific targeting of molecular abnormalities will ultimately lead to myocardial-specific treatment for ADCM patients who do not experience spontaneous recovery of function.

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DISCUSSION

Calkins, Baltimore: Great talk. I want to ask two questions. The first has to do with stress-induced cardiomyopathy. In your studies, was that sort of unique subset excluded, or was that not on your radar screen? And do you think that played a role in your results? The second thing is the whole definition of acute onset dilated cardiomyopathy. Whether patients have had it for 5 years and it presents acutely or whether it really was there for many years — how did you tease that out in your studies?

Dec, Boston: So, great questions. Stress-induced cardiomyopathy or takotsubo was certainly rampant during this period. We did exclude people that had evidence for it by echo, so we didn't include any of those. I think there were about a half dozen people that were excluded from that. With regard to the chronicity versus acuity, that's one of the problems with this whole field is that, you know, somebody could well have had a mild cardiomyopathy for a decade and some intercurrent problem tips them over so they become symptomatic. We just had to go, when they presented, and tried, as best we could, judge the symptom duration. So it's a very, very weak way to do it.

Mann, St. Louis: Bill, wonderful talk. I am going to ask you the question I always get asked, because I am learning from you now. What do you do with these patients after they normalize their left ventricular function? The question is whether you should leave them on medicines or not leave them on medicines. We don't really have data. I think your data are the best. And then the German group, I think, also suggests that the amount of end-organ damage might precondition that. But what do you tell your patients after their EF comes back?

Dec, Boston: That's certainly the $64,000 question, because they always ask and they want to come off drugs. I think if it's something that you know is reversible and if

you keep the stimulant away, if it's alcohol cardiomyopathy or, you know, peripartum cardiomyopathy, I wean them off medicines if their hearts are normal and stay normal for at least a year. For the idiopaths like this, if they have no evidence for structural abnormalities, I will often do either an MRI to see if there is any fibrosis there and how much or a stress echo to see what their contractile reserve is. If they have absolutely completely normal tests, I usually will wean them back to one drug. When I wean them off completely, I've had a recurrence rate of about 4% to 5% when they end up on nothing within the next 2 years. So I like to have some background therapy, unless all of their studies are completely normal and they want to have kids or get off the drugs for some other reason.

Mann, St. Louis: We've started using dobutamine stress as a way to sort of cut it and not enough data yet but. . .

Dec, Boston: Yeah, I really think that's the way to go. I mean the goal, obviously, is to get people off the drugs if they don't need them, but you don't want to have a relapse either.

Mushlin, New York: I really enjoyed the talk, too, and appreciate the statistical analysis that you and your group have been carrying out in this changing condition. So I have two interrelated questions. The first one is, how much of the variants and outcomes are explained by the multivariate model? And related to that and I think more importantly is, can you — and have you — tried to parse out the change in outcome that's associated with new treatment changes of the time?

Dec, Boston: Great question. So looking at what the multivariate modeling tells us, it predicts about 50% to 55% of likely recovery. So we are just barely halfway there. So there are a lot of other factors; we don't have a model. There is no good way to know what kind of therapy has any influence, because everybody pretty much gets the standard treatment. So there is no way to parse that out right now.